JACC
Journal of the American College of Cardiology/*Contents in brief*

DECEMBER 1986 VOLUME 8 NUMBER 6

Journal of the American College of Cardiology (ISSN 0735-1097) is issued monthly in two indexed volumes per year by Elsevier Science Publishing Co., Inc., 52 Vanderbilt Avenue, New York, NY 10017. Printed in USA at 2901 Byrdhill Road, Richmond, VA 23228. Subscription prices per year: institution, $100.00; individual $69.00, interns and residents, $43.00. Outside USA, add $35.00 for surface postage and handling. For air delivery to USA, Canada and Mexico, add $75.00; in Europe, $65.00 (via surface air-lift); to Japan, $95.00; and to rest of world $225.00. Single copy price, $16.00. Second-class postage paid at New York, NY and at additional mailing offices. Postmaster: Send address changes to *Journal of the American College of Cardiology*, Elsevier Science Publishing Co., Inc., 52 Vanderbilt Avenue, New York, NY 10017.

JACC Vol. 8, No. 6
December 1986:1271–6

Effect of Nifedipine on Recurrent Stenosis After Percutaneous Transluminal Coronary Angioplasty

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This double-blind, randomized study evaluated the effect of nifedipine on restenosis after coronary angioplasty. Two hundred forty-one patients with dilation of 271 coronary sites were randomized at the time of hospital discharge to receive nifedipine, 10 mg (123 patients), or placebo (118 patients) four times daily for 6 months. No patient was known to have coronary artery spasm. The mean duration of therapy was 4.4 ± 2 (mean ± SD) months for nifedipine and 4.3 ± 2 months for placebo. A restudy angiogram was available in 100 patients (81%) in the nifedipine group and 98 patients (83%) in the placebo group.

A recurrent coronary stenosis was noted in 28% of patients in the nifedipine group and in 29.5% of those in the placebo group (p = NS). The mean diameter stenosis was 36.4 ± 23% for the nifedipine group and 36.7 ± 23% for the placebo group (p = NS). By pill count, 78% of patients receiving nifedipine and 82% of those receiving placebo complied with the study drug regimen. Coronary stenosis recurred in 33% of patients in the placebo group and in 29% of patients in the nifedipine group who complied with the regimen and had angiograms (p = NS). In conclusion, the study did not demonstrate a significant beneficial effect of nifedipine on the incidence of recurrent stenosis after successful percutaneous transluminal coronary angioplasty.

(J Am Coll Cardiol 1986;8:1271–6)

Percutaneous transluminal coronary angioplasty (1) has gained increased acceptance as a safe and effective therapy for coronary artery disease. Long-term benefit of coronary angioplasty has been limited in some patients, however, by the recurrence of stenotic lesions (2,3). Various adjunctive therapies such as aspirin and other antiplatelet agents have been proposed to decrease such recurrences (4,5).

Coronary artery spasm has been observed after angioplasty (6–8) and subclinical spasm was thought to be causally related to restenosis (6,8). Spasm usually occurs during the first 2 months after angioplasty (6) and most restenoses are identified between 2 and 6 months (2,9). The effectiveness of nifedipine in the treatment of coronary artery spasm (10–12) has encouraged the routine use of nifedipine and other calcium blocking drugs in the months after coronary angioplasty. This practice has been maintained although there has been little evidence that such treatment is of benefit in reducing lesion recurrence. Our study was undertaken to prospectively evaluate the effectiveness of nifedipine in preventing restenosis in patients after successful coronary angioplasty.

Methods

Study patients. Between July 23, 1982 and December 7, 1983, coronary angioplasty was attempted at 1,932 vessel sites in 1,710 patients. All patients had characteristic symptoms or objective clinical evidence of myocardial ischemia based on spontaneous electrocardiographic T wave changes or stress testing data. The angioplasty procedure was performed by the femoral route using a standard technique described elsewhere (13,14). Successful dilation (20% reduction in stenosis diameter) was achieved in 1,748 lesions (90.5%). Patients aged 21 to 75 years without reocclusion within 48 hours were considered candidates for the study. Patients were excluded if they had a history of adverse response to any calcium antagonist, documented coronary artery spasm or incomplete revascularization necessitating antianginal medication using a calcium antagonist. Two

*Publication posthumous.

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Manuscript received January 22, 1986; revised manuscript received June 10, 1986, accepted June 26, 1986.

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0735-1097/86/$3.50

JACC Vol. 8, No. 6
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hundred forty-one patients with 271 dilated coronary lesions agreed to participate in the study. The study was approved by the Ethics Committee of this institution and all patients gave written informed consent.

Study design. The study was performed double-blind with patients randomized at 48 hours after angioplasty to either 10 mg of nifedipine or placebo four times daily. Immediately before arterial dilation, patients received 10 mg of nifedipine and 0.4 mg of nitroglycerin sublingually, and 200 μg of intracoronary nitroglycerin. All patients received calcium antagonist treatment for 48 hours after the procedure. The study drugs were provided for 6 months by the manufacturer as uniform capsules in numbered lots. These were grouped by a computer-generated random code in blocks of 10. All patients except three (two taking nifedipine, one taking the placebo) received 325 mg aspirin daily. Other medications prescribed during the follow-up period were determined by primary physicians.

Follow-up protocol. Patients were given a 2 month supply of the study drug at hospital discharge. The remaining 4 month supply was provided after compliance was checked at 1 month. All patients were questioned before angioplasty regarding the nature, frequency and duration of their chest pain. Questionnaires regarding angina, work status and activity level were sent to patients after 3 and 6 months of therapy. Recurrence of chest pain similar to that experienced before arterial dilation was considered positive evidence of restenosis regardless of the severity, duration or frequency of pain. These data were obtained from written questionnaires sent to all patients.

Compliance with the study drug regimen was evaluated by a count of unused capsules returned after 1 and 6 months of therapy. Patients were judged compliant who took at least 75% of their medication until either 6 months of therapy was completed or symptoms suggesting recurrent stenosis developed and early discontinuation of the study drug was required.

All patients and referring physicians were contacted to arrange a restudy angiogram after completion of therapy. Letters at 6 months, follow-up telephone calls and repeat mailings were utilized. Follow-up angiograms performed elsewhere were forwarded to our institution for analysis. When follow-up arteriography was not available, exercise test results were forwarded to our institution. A positive follow-up exercise test was defined as a reversible scintigraphic defect (thallium) in the vascular distribution of the dilated artery or 1 mm of horizontal or downsloping ST segment depression of 80 ms or more past the J point in the electrocardiogram.

Restenosis. Restenosis was defined as the loss of at least 50% of the gain in luminal diameter accomplished at initial dilation. An additional analysis of restenosis in each group defined restenosis as a lesion of 50% or greater in diameter on the restudy angiogram. Stenoses were measured in at least two projections using a computerized caliper system. Diameter stenosis was calculated as the mean of measurements in two or three available projections.

Statistical analysis. Data from the 241 patients were analyzed by intention to treat as well as by groups judged compliant with the study drug regimen. Recurrence rates were determined by the total number of lesions dilated (271 lesions) as well as by the total number of patients (241 patients). Patients with dilation of multiple sites were considered to have recurrence if any one site dilated had a recurrence. Comparison of discrete variables was done using a chi-square analysis. Continuous variables were compared using an unpaired or paired Student's *t* test as appropriate. A probability (p) value of less than 0.05 was considered significant.

Table 1. Baseline Characteristics of 241 Patients

	Nifedipine	Placebo	p Value
Patients (n)	123	118	
Age (yr)*	53 ± 9	55 ± 10	NS
Sex: male	106 (86%)	103 (87%)	NS
Previous myocardial infarction	32 (26%)	24 (20%)	NS
Duration of angina (mo)*	11 ± 21	8 ± 16	NS
Vessel dilated (n)			
LAD	67 (49%)	82 (61%)	NS
LCx	21 (16%)	25 (18%)	NS
RCA	48 (35%)	28 (21%)	<0.05
Total	136	135	
Lesion length (mm)*	6.5 ± 4	6.4 ± 4	NS
Eccentric lesion	48 (36%)	60 (44%)	NS

*Values are means ± SD. LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; RCA = right coronary artery.

Results

Baseline characteristics (Tables 1 and 2). The nifedipine and placebo treatment groups were comparable in age, sex, previous angina history and history of myocardial infarction (Table 1). Twenty more right coronary artery lesions were dilated in the nifedipine group and 15 more left

Table 2. Angioplasty Results in 241 Patients

	Nifedipine (n = 123)	Placebo (n = 118)	p Value
Diameter stenosis (%)			
Before PTCA	73 ± 13	69 ± 14	<0.05
After PTCA	23 ± 11	23 ± 10	NS
Pressure gradient (mm Hg)			
Before PTCA	48 ± 13	52 ± 14	<0.05
After PTCA	11 ± 6	12 ± 7	NS

PTCA = percutaneous transluminal coronary angioplasty.

anterior descending artery lesions in the placebo group (Table 1). The extent of disease was comparable in both groups, with a higher percent diameter stenosis in the nifedipine group but a higher transstenotic pressure gradient in the placebo group (Table 2). Results of dilation were similar in both groups as measured by percent diameter stenosis and transstenotic pressure gradient. The procedure resulted in a mean decrease in diameter stenosis of 50% in the nifedipine group and 46% in the placebo group. Of the 136 lesions in the nifedipine group, the immediate postdilation residual diameter was 30% or less in 111 patients, 31 to 40% in 20 patients, 41 to 50% in 3 patients and greater than 50% in only 2 patients. Of the 135 lesions in the placebo group the residual diameter was 30% or less in 104 patients, 31 to 40% in 23 patients and 41 to 50% in 8 patients. The incidence of intimal tears was also similar, occurring in 22% of patients receiving nifedipine and 21% of those receiving placebo. Multivariate, stepwise regression analysis of baseline factors showed that lesions in the left anterior descending and right coronary arteries were associated with a higher rate of restenosis ($p = 0.02$). In addition, patients with a shorter duration of angina tended to have a higher rate of restenosis ($p = 0.09$).

Compliance and duration of therapy. Compliance with the study drug regimen was similar in both groups. Ninety-six patients (78%) in the nifedipine group and 97 (82%) of the placebo group took at least 75% of the prescribed dose of the study drug. Therapy was continued in these patients for 6 months or until symptoms suggesting ischemia required early discontinuation of therapy. Noncompliance was due to side effects in 22 patients receiving nifedipine and 11 patients receiving placebo ($p < 0.1$). Other causes of noncompliance were the patient's desire to leave the study or lack of 75% compliance with drug dosage (five patients taking nifedipine, 10 patients taking the placebo, $p = NS$).

The mean duration of therapy with the study drug in the overall nifedipine and placebo groups was not statistically different (4.4 ± 2 and 4.3 ± 2 months, respectively). Therapy was terminated before 6 months in 41% of the total nifedipine group and 43% of the total placebo group. Among compliant patients, 25% assigned to nifedipine and 32% assigned to placebo discontinued the drug before 6 months. The mean duration of therapy for these patients tended to be longer in the nifedipine group (5.3 ± 1 months) than in the placebo group (4.9 ± 2 months) ($p < 0.1$). Although the total number of patients who stopped the study drug in the first 2 months was similar for the two groups (35 taking nifedipine, 38 taking placebo, $p = NS$), during this period, patients in the placebo group were more likely than those in the nifedipine group to discontinue the regimen because of chest pain (18 versus 8 patients, $p < 0.1$). Patients taking nifedipine were more likely to discontinue the drug during these initial 2 months because of side effects (27 patients) than because of chest pain.

Table 3. Incidence of Recurrence of Coronary Stenosis

	Nifedipine	Placebo
A. All Patients		
Angiography	28/100 (28%)	29/98 (29.5%)
Exercise stress test	2/11 (18%)	1/12 (8%)
Total	30/111 (27%)*	30/110 (27%)*
B. Compliant Patients		
Angiography	24/84 (29%)	28/84 (33%)
Exercise stress test	1/8 (12%)	1/8 (12%)
Total	25/92 (27%)*	29/92 (31.5%)*

*p = NS.

Restenosis (Table 3). A restudy coronary angiogram was available in 100 (81%) of the 123 patients taking nifedipine at 6.5 ± 2 months after coronary angioplasty and in 98 (83%) of the 118 patients taking placebo at 6.6 ± 3 months after angioplasty. A recurrent stenosis was noted in at least one of the dilated sites in 28 (28%) of the 100 patients receiving nifedipine and 29 (29.5%) of the 98 patients receiving placebo for whom an angiogram was available. With the inclusion of exercise test data, objective information was available for 111 (90%) of 123 patients receiving nifedipine and 110 (93%) of 118 of those receiving placebo. Including all such objective data, the recurrence rate was 27.0% (30 of 111) in the nifedipine group and 27.3% (30 of 110) in the placebo group (Table 3A).

Restenosis was also defined and analyzed as a lesion 50% or greater in diameter, which may sometimes better reflect hemodynamic significance. The frequency of recurrence remained similar between the two groups with 26 patients receiving placebo and 27 patients receiving nifedipine having at least one lesion noted on restudy arteriography.

Multiple sites were dilated in 29 (14%) of the 241 patients, totaling 271 lesions. Distribution of these patients was similar in both treatment groups (Fig. 1). The incidence of recurrent stenosis per lesion, including only those with objective follow-up, was 26% (32 of 124) of the nifedipine group and 27% (34 of 124) of the placebo group ($p = NS$). The mean diameter stenosis for all lesions with follow-up angiograms was 36.4 ± 23% in the nifedipine group and 36.7 ± 23% ($p = NS$) in the placebo group. The distribution of the values obtained on the restudy angiogram also did not differ significantly.

When only those patients judged compliant with therapy were analyzed, there remained no significant difference in restenosis (Table 3B). A recurrent stenosis was identified by objective data in 27% (25 of 92) of patients in the nifedipine group and 31% (29 of 92) of those in the placebo group ($p = NS$). When individual vessel sites were analyzed, 25% (26 of 103) of sites in the nifedipine group and 32% (33 of 103) of sites in the placebo group showed re-

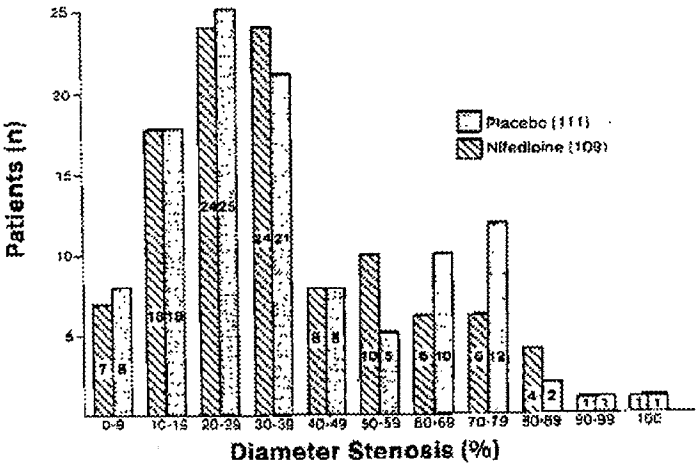

Figure 1. Frequency distribution of 220 patients in different coronary diameter stenosis groups at the time of the restudy angiogram. Values under each bar denote the number of patients.

currence (p = NS). The mean diameter stenosis was 36 ± 22% for the nifedipine group and 38 ± 24% for the placebo group (p = NS).

Chest pain was reported by 52 (42%) of 123 patients in the nifedipine group and 55 (47%) of 118 patients in the placebo group (p = NS). Among patients who complied with therapy, complaints of chest pain were similar: 46% (44 of 96) for the nifedipine group and 49% (47 of 97) for the placebo group. Chest pain, however, was unreliable in predicting restenosis. Among patients for whom both angiographic follow-up and chest pain data were available, only 40% (19 of 47) of those in the nifedipine group and 49% (23 of 47) of those in the placebo group complaining of chest pain were found to have recurrence. Among patients who did not report chest pain, 14.6% (7 of 48) of those receiving nifedipine and 12.5% (6 of 48) of those receiving placebo had recurrent stenoses.

Table 4. Side Effects in 241 Patients

	Nifedipine* (n = 123)	Placebo* (n = 118)
Peripheral edema	12 (9)	2 (1)
Dizziness	5 (4)	0
Mood change	5 (4)	0
Nausea	3 (3)	5 (5)
Palpitation	1 (1)	0
Hypertension	1	1 (1)
Headache	0	1 (1)
Weakness	0	1 (1)
Muscle cramps	0	1 (1)
Nocturia	1 (1)	0
Hiccup	0	1 (1)
Total	28 (22)	12 (11)†

*Number of patients in whom the drug was discontinued is given in parentheses. †p < 0.05.

Side effects with the study drug (Table 4). These were more common in the nifedipine than in the placebo group. Twenty-three percent of the former (28 of 123) and 10% (12 of 118) of the latter reported adverse reactions. Side effects severe enough to require discontinuation of the study drug also tended to be greater in the nifedipine group. The most common complaints by patients treated with nifedipine were peripheral edema, dizziness and mood changes; nausea was most often cited in the placebo group.

Discussion

Previous reports (6,7,8,15) have noted a higher rate of recurrent coronary stenosis in patients with coronary artery spasm after successful coronary angioplasty. It has been suggested that unrecognized coronary spasm in many patients after angioplasty may contribute to restenosis at the dilated site. Accordingly, large numbers of patients were and are still receiving calcium blocking drugs as routine discharge medication. This study demonstrated no significant effect of nifedipine therapy on either mean residual coronary stenosis on follow-up angiography or incidence of patients with recurrent stenoses. This finding pertained when both the total group and only patients with proved compliance with the study drug regimen were analyzed.

Influence of baseline characteristics on restenosis. Although there were some minor differences in the baseline characteristics of the two randomized groups, these do not appear to have affected the results. The mean percent stenosis before angioplasty was higher in the nifedipine group;

however, this is balanced by the mean pressure gradient before angioplasty, which was higher in the placebo group. In the subset of patients judged compliant with therapy, the duration of angina in the placebo group was significantly shorter ($p < 0.05$). This has been associated with an increased recurrence rate and would tend to favor restenosis in the placebo group. Other factors identified with an increased recurrence rate were similar in both study groups. These include male sex (2), no previous myocardial infarction (2), increased final coronary pressure gradient (2,16) and absence of intimal tear (16).

Comparison with previous studies. Other centers have also evaluated the effect of calcium antagonist treatment after angioplasty. Our results concur with the laboratory findings of Faxon et al. (17). They demonstrated a comparable recurrence of stenosis for control versus nifedipine treatment in atherosclerotic rabbits 4 weeks after experimental angioplasty. In a preliminary report Val et al. (15) compared sulfinpyrazone and diltiazem with sulfinpyrazone treatment alone after successful coronary angioplasty. They found no improved clinical or angiographic outcome in patients treated with diltiazem. Recently in a smaller, prospective, although nonblinded trial, Corcos et al. (18) reported no decrease in the incidence of recurrent stenosis with the addition of diltiazem to platelet inhibitor therapy. Stenosis recurred in only 7 of 50 coronary segments dilated in the diltiazem group and 10 of 53 segments in the control group. They required a restudy stenosis of 70% or greater to define a recurrent stenosis, which would appear to explain their lower incidence of restenosis.

Chest pain after angioplasty. There was no significant difference in the incidence of chest pain between the nifedipine and placebo groups. In addition, the unreliability of chest pain history as a predictor of recurrent stenosis was the same in both groups. Among our patients reporting chest pain, this finding was unreliable in predicting a recurrent stenosis, and in other patients the absence of chest pain was unreliable in predicting continued success. These findings concur with those of the National Heart, Lung, and Blood Institute Coronary Angioplasty Registry (2). However, there was a greater tendency for the onset of chest pain to occur during the first 2 months after angioplasty in the placebo group. It is possible that the antianginal effect of nifedipine delayed the recurrence of symptoms although not the incidence of lesion restenosis.

Clinical implications. We were unable to identify a beneficial effect of nifedipine in decreasing the incidence or degree of restenosis after coronary angioplasty. This implies that coronary artery spasm does not play a significant role in the pathogenesis of such restenosis after angioplasty in the general patient population. Our patient group did not include those with clinically apparent coronary artery spasm, however, and previous reports (6–8,19,20) have identified a high incidence of restenosis in these patients. Patients should be screened closely for evidence of coronary artery spasm and such patients treated with aggressive medical therapy. In patients without coronary artery spasm, we can no longer justify calcium antagonist therapy on a routine basis after coronary angioplasty.

We gratefully acknowledge the assistance of Kathy Galan, RN and Lila Gershon, RN for data acquisition, Johnny Tate and George Cutsonis for computer programming and statistical assistance, Diana Williams for typing the manuscript and Linda Greene for editorial help.

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Inter Partes Reexamination No. 95/001,095
Declaration of Antonios G. Mikos, Ph.D.
Exhibit 9

Cardiovasc Intervent Radiol (1996) 19:176–180

CardioVascular and Interventional Radiology

Comparison of Self-Expanding Polyethylene Terephthalate and Metallic Stents Implanted in Porcine Iliac Arteries

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Abstract

Purpose: Comparison of the biocompatibility of self-expanding polyethylene terephthalate (PET) stents with self-expanding metallic stents (Wallstents).

Methods: Diameter- and length-matched PET stents and Wallstents were symmetrically implanted in the paired iliac arteries of 13 crossbred domestic swine. Stent deployment was studied angiographically and with intravascular ultrasound immediately after stent implantation. The angiographic stented lumen diameter was measured using quantitative vessel analysis before, immediately after stenting, and at 6-week follow-up. Cross-section histopathology and area morphometry were performed.

Results: Immediately poststenting, intravascular ultrasound revealed proximal dislocation of 5 of the 13 PET stents, whereas all metal stents were firmly embedded at the implantation site. At 6-week follow-up, three of the remaining PET stents were totally or subtotally occluded by organized thrombus, whereas all metal stents were patent. Compared with immediately poststenting, the angiographic lumen diameter within the five remaining PET stents was reduced by 30%, and that of the metallic stents was virtually unaltered ($p < 0.02$). This observation was confirmed by postmortem morphometry, wherein the PET-stented vessel segments a diameter stenosis of 40% was measured vs only 9% in the metallic stents ($p < 0.0001$).

Conclusion: PET-stent deployment is difficult to control due to the lack of radiopacity of this stent. PET stents seem to be more thrombogenic and lead to significantly more neointimal proliferation than metallic stents.

Key words: PET stents—Metallic stents—Angiography—Ultrasound—Neointimal hyperplasia thrombosis

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Widespread clinical use of the current metallic endovascular stents is still hampered by acute occlusions related to the thrombogenicity of the stent material [1–3] and by late restenosis due to neointimal hyperplasia [3, 4]. In addition, intracoronary delivery of metallic stents is sometimes hampered by their limited flexibility, a prerequisite for successful negotiation of acute angles within the coronary tree. To overcome these disadvantages of metallic stents, the mechanical properties and biocompatibility of a number of alternative materials are currently under investigation. In the search for new materials suited for stenting, polyethylene terephthalate (PET) was chosen first because of its widespread use as angioplasty-balloon material, its ready availability, and because its biocompatibility has been extensively studied when used in vascular grafts [5].

Recently, Murphy et al. [6] implanted 11 PET self-expanding stents in porcine coronary arteries and observed only one acute thrombotic occlusion even without an adequate antithrombotic regimen. However, at 4–6 weeks, a chronic foreign body inflammatory proliferation around the stent filaments did occur and an extensive neointimal response resulted in complete coronary vessel occlusion in all stents. We previously implanted 10 self-expanding PET stents in porcine peripheral arteries. At 6 weeks, histopathology showed thrombotic occlusion of three stents and only moderate neointimal proliferation in the remaining patent stents [7]. Van der Giessen et al. [8] implanted eight self-expanding, braided-mesh PET stents in porcine peripheral arteries and, after 4 weeks, repeat angiography revealed that only one stent was subtotally occluded. At autopsy, two other stents proved to be located in the aortic bifurcation and the 5 remaining stents were patent and showed only minor neointimal proliferation.

Faced with these conflicting observations concerning mechanical properties and biocompatibility of PET material, we decided to compare this polymer against a metallic stent (Wallstent, Schneider Europe, Bülach,

Switzerland), a stent material currently used in clinical practice.

Materials and Methods

Devices

The PET stent (Schneider) consisted of a tubular mesh of 24 filaments. The thickness of the filaments was 0.2 mm and the unconstrained diameter and length of this stent were 6 mm and 20 mm, respectively. The Wallstent (Schneider) consisted of a tubular mesh of 20 cobalt-based alloy filaments. The diameter of the filaments was 0.09 mm and the unconstrained diameter and length of this stent were 5 mm and 20 mm, respectively (Fig. 1). The individual filaments of these prostheses were not fixed at the cross-points and, therefore, could freely move. All stents were constrained and mounted on a specially designed 9 Fr rolling membrane device and sterilized using ethylene oxide before use.

Experimental Protocol

A total of 13 domestic crossbred pigs of both sexes (weight 20–25 kg) were used. All animals were treated and cared for in accordance with the National Institute of Health Guide for the care and use of laboratory animals and were fed on a standard natural grain diet without lipid or cholesterol supplementation. The pigs were sedated with intramuscular azaperon 0.1 ml/kg (Stresnil, Janssen Pharmaceuticals, Beerse, Belgium) before general anesthesia was induced with intramuscular (5 mg/kg) followed by intravenous (10 mg/kg/h) ketamine (Ketalar, Parke-Davis NV, Warner-Lambert, Zaventem, Belgium) and intravenous pancuronium (Pavulon, Organon NV, Oss, Holland) at a rate of 0.4 mg/kg/hr. The pigs were intubated and ventilated (Mark 7A, Bird Company, Palm Springs, CA, USA) using a mixture of 20% vol pure oxygen and 80% vol of room air. Ventilation was adjusted by frequent blood gas analysis in order to maintain a minimum PaO_2 of 100 mmHg and physiologic $PaCO_2$ and pH parameters. The electrocardiogram, as well as blood pressure and body temperature, were continuously monitored throughout the procedure. An external carotid artery was surgically exposed and a 9 Fr intraarterial sheath was introduced over a 0.035" wire. Heparin (5000 IU) and acetyl salicylic acid (500 mg) were administered intravenously as a bolus. Furthermore, heparin (400 IU/hr) was given as a continuous infusion during the procedure. The iliac arteries were visualized using an 8 Fr El Gamal catheter, and iohexol (Omnipaque, Nycomed, Oslo, Norway) was used as the contrast agent. In each pig, one PET and one metal stent were symmetrically deployed in the midpart of each common iliac artery. After implantation of the stent, vessel status was checked angiographically as well as by intravascular ultrasound. If insufficient stent deployment was demonstrated, adjunctive balloon inflations were performed until an optimal result was obtained. The carotid arteriotomy was repaired and the dermal layers were closed using standard techniques. The animals were returned to a postoperative recovery area and further observed in the university animalium. No antiplatelet agents or additional anticoagulants were administered during follow-up.

Six weeks later, using the same instrumentation technique as during stent implantation, a control angiogram of the stented vessels was obtained and the pigs were subsequently sacrificed using an intravenous bolus of 10 ml oversaturated potassium chloride. At that time their mean weight was 63 kg.

Intravascular Ultrasound (IVUS) and Quantitative Angiography

Immediately after stent implantation, the ultrasound device (Interpret, Intertherapy Inc, Costa Mesa, CA, USA) was advanced over the 0.014" guidewire into the iliac artery. The ultrasound device consists of a 4.9 Fr diameter cable with a 20 MHz radiopaque transducer at the distal tip. To protect the arterial lumen, this device was introduced through a 1.9-mm-diameter plastic sheath conveniently advanced as a monorail system over the guidewire and positioned in the distal part of the artery. Then a motor-driven unit withdrawing the ultrasound device at a constant speed of 0.50 mm/sec over the region of interest was engaged while the introducing sheath remained in place. Ultrasound images were continuously recorded on super VHS videotape together with fluoroscopic sequences documenting the position of the ultrasound transducer within the artery. During withdrawal of the ultrasound device a total of 140 ultrasound images were digitally stored in the computer memory at a rate of six frames/min and sagittal sections of the artery were automatically obtained. Subsequently, the ultrasound subassembly and introducing sheath were removed and a follow-up angiogram was performed.

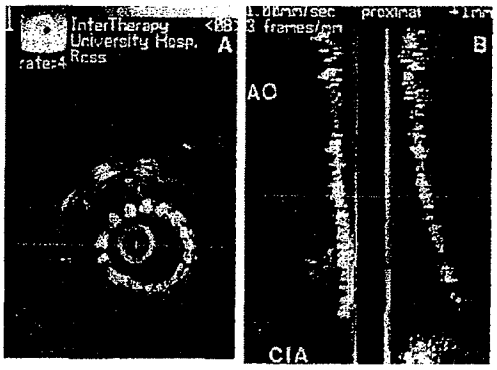

Fig. 1. Stent (PET) dislocation demonstrated by intravascular ultrasound. A A cross-section at the level of the aortic bifurcation shows the deployed stent floating in the aorta (arrowheads). B Sagittal section at the level of the aortic bifurcation. The distal part of the stent is still attached at the ostium (arrowhead) of the common iliac artery (CIA) and the proximal part is floating in the aorta (AO).

Before and immediately after stenting and at 6-week follow-up, angiographic analysis was performed using the Polytron 1000-system that was earlier validated in vitro and in vivo [9–11]. A metal bar was used as the calibration device. Angiographic diameter measurements before and immediately after stenting were performed at three different sites (proximal, mid, and distal part of the stent). At 6 weeks, angiographic measurement was performed at the most stenosed site observed on the angiogram.

Histopathology and Morphometry

After being sacrificed, the stented iliac artery segments were carefully dissected and fixed in 2% formalin. The stent filaments were removed using a stereomicroscope (so as not to distort or damage the artery). Cross-sections from each arterial segment were stained with hematoxylin-eosin, elastin von Gieson, and Masson's trichrome stain and carefully examined by light microscopy by one of the authors (EV).

Damage of the vascular wall was graded as intact internal and external elastic membrane, or disruption of the internal elastic membrane but intact external elastic membrane, or disruption of both the internal and external elastic membranes. Neointimal proliferation within the stented segments was visually estimated and the predominant histological event leading to intimal proliferation was studied. Finally, morphometric analysis was performed using a computerized morphometry program (CBA 8000, Leitz, Solms, Germany). Measurements of maximal intimal thickness, lumen area, and the area inside the internal and external elastic lamina were performed at the most reactive arterial site, as visually observed.

Statistics

Arteriographic measurements before, immediately after, and 6 weeks after stent implantation were compared using the paired *t*-test. The unpaired *t*-test was used for intergroup comparison. Nominal variables were compared using the Chi-square tests. A p value of < 0.05 was considered statistically significant.

Results

A total of 13 PET and 13 metallic self-expandable stents were symmetrically implanted in the iliac arteries of 13 pigs. All implantations were uneventful and control angiography immediately after stent implantation showed a patent lumen, without dissection or spasm.

IVUS and Quantitative Angiography

IVUS performed immediately after stent implantation revealed a dislocation of 5 of the 13 PET stents (Fig. 1), whereas all metallic stents were firmly embedded at the implantation site. The pullback of the IVUS catheter located two PET stents near the ostium of the iliac artery and three PET stents in the aortic bifurcation. Furthermore, IVUS demonstrated inadequate deployment of another four PET stents and of two metallic stents. However, after adjunctive balloon angioplasty using a 5-mm angioplasty balloon for both plastic and metal stents, repeat IVUS examination showed a perfect alignment of all stent filaments.

At 6 weeks the angiogram obtained before sacrifice of the pigs showed that all metallic stents were patent without intrastent stenosis. Of the eight correctly implanted PET stents, two were totally and one was subtotally occluded, whereas the others showed some degree of intrastent narrowing.

Angiographic vessel diameters, as well as the intrastent luminal diameters, measured immediately after stent implantation and at 6 weeks, are presented in Table 1. Between the stent materials, pre- and immediately postimplantation, there was no significant difference in these variables, but at 6 weeks the lumen of the five well-implanted and patent PET stents had narrowed from 4.40 ± 0.70 mm to 3.24 ± 1.21 mm ($p = 0.03$) resulting in a significant difference ($p = 0.002$) from that of the metallic stents, which was virtually unaltered.

Histopathology and Morphometry

At postmortem histopathological examination the internal elastic lamina appeared to be disrupted by 10 of the 13 metallic stents and by 7 of the 8 PET stents but the external elastic lamina was intact in all vessel segments. Histopathology of the metallic stents revealed only a mild neointimal fibromuscular proliferation covering the stent filaments (Fig. 2). In the PET stents this neointimal fibromuscular proliferation was more pronounced (Figs. 3 and 4). In three PET stents, histopathological examination revealed a mild histiolymphocytic cellular reaction surrounding the stent filaments. Histopathological examination of the three occluded PET stents showed a recanalized, organized thrombus within the vessel lumen. Morphometry was performed on the 13 metallic and the 5 patent PET-stented vessel segments. These results are presented in Table 2 and largely confirmed the angiographic observations that PET material induced more neointimal hyperplasia leading to more severe luminal narrowing when compared with metallic stents.

Table 1. Angiographically measured mean diameters (mm) of the stented vessel segments

Stent type	Prestenting	Immediately poststenting	At 6 weeks
Metal ($n = 13$)	4.41 ± 0.84[a]	4.52 ± 0.58	4.50 ± 0.63
PET ($n = 5$)	4.34 ± 0.65	4.40 ± 0.70	3.24 ± 1.21[b]

[a] Mean ± standard deviation
[b] $p < 0.02$ when compared with metallic stents at 6 weeks; $p < 0.03$ when compared with immediate poststenting diameter

Discussion

The present study examined the feasibility of implanting self-expanding PET stents in normal porcine iliac arteries and compared, at follow-up, the degree and histopathological substrate of the vessel narrowing with that induced by commercially available, metallic, self-expanding stents (Wallstents).

For comparison of periprocedural complications, angiography and IVUS were performed immediately after stent implantation. For our study IVUS was especially important since the poor or absent radiopacity of the metallic and PET stents, respectively, virtually excluded their radiographic imaging. IVUS performed immediately after stent implantation revealed dislodgement of the stent from the implantation site in 5 of the 13 PET stents. The stents were found proximal to the implantation site suggesting that inadequate radial force impeded their firm embedding in the vascular wall so that, during retrieval of the delivery system, dislocation did occur. Van der Giessen et al. [8] also reported that, at autopsy, two of eight similar PET stents implanted in porcine iliac arteries were found in the aortic bifurcation but, in the absence of IVUS control, they suggested that this was most likely due to an incorrect placement of the stent. Clearly related to the same mechanical deficiency of the PET material, 4 of the 8 remaining PET stents were inadequately deployed vs only 2 of the 13 metallic stents. All these IVUS observations clearly stress the importance of radio-

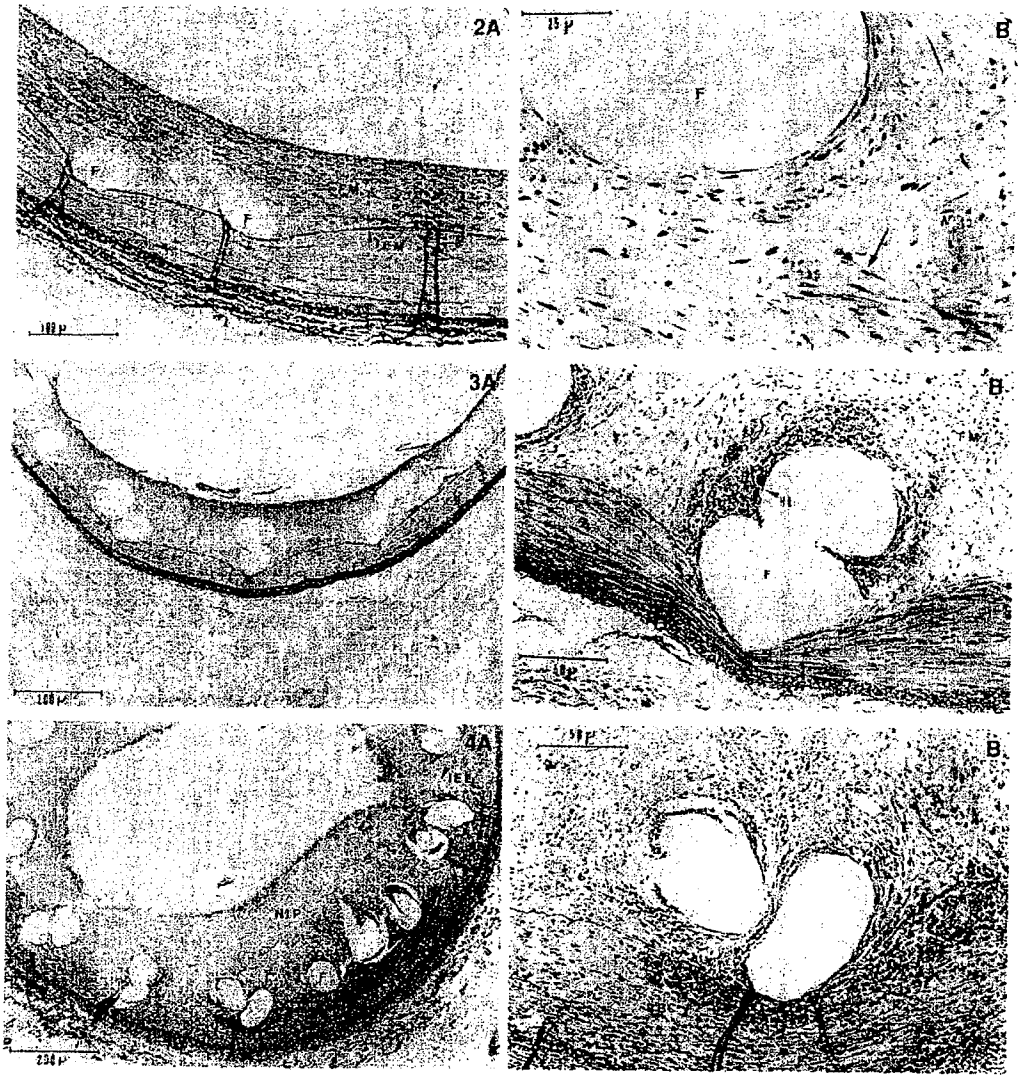

Fig. 2. Cross-section of a vessel segment stented with the Wallstent. The internal elastic membrane (IEM) is displaced by the stent filaments (F) which are surrounded by a mild fibromuscular (FM) proliferation of spindle cells (arrowhead). There is no foreign body inflammatory response. **A** Elastica von Gieson stain, magnification ×250 (Barr = 100 μm). **B** Hematoxylin and eosin stain, magnification ×1000 (Barr = 25 μm).

Fig. 3. Photomicrograph of a vessel segment stented with a polyethylene terephthalate self-expanding stent. **A** The intact internal elastic membrane is displaced by stent filaments. The neointimal proliferation is mild but more pronounced compared with that induced by the metallic stent (magnification ×125); Barr = 200 μm). **B** Higher magnification (×500) demonstrates a histiolymphocytic (HL) infiltrate surrounding the stent filaments (F). More distal to the filaments the neointimal proliferation contains fibromuscular (FM) cells.

Fig. 4. Photomicrograph of another vessel segment stented with a polyethylene terephthalate stent. **A** Pronounced vessel-wall injury caused disruption of the internal elastic lamina (IEL) (arrowhead). Note the pronounced neointimal proliferation (NIP) leading to severe luminal narrowing. F = Stent filaments (Elastica von Gieson ×125; Barr = 200 μm). **B** The higher magnification (×500) demonstrates accumulation of red blood cells (RBC) below the stent filaments. Distal to the stent filaments, the neointima contains abundant fibromuscular cells (arrowheads), but no foreign body reaction.

Table 2. Postmortem morphometry

Measurement	Metal (n = 13)	PET (n = 5)	p value
Luminal area (mm^2)	8.94 ± 3.03*	3.07 ± 2.15	0.003
Luminal diameter (mm)	3.33 ± 0.57	1.90 ± 0.65	0.0001
EEL area (mm^2)	12.48 ± 3.00	10.89 ± 5.00	0.438
EEL diameter (mm)	3.96 ± 0.47	3.56 ± 1.01	0.275
Area stenosis (%)	16.18 ± 9.32	59.45 ± 14.90	0.0001
Diameter stenosis (%)	8.52 ± 5.50	40.17 ± 22.19	0.0001
Hyperplasia (mm)	0.29 ± 0.15	1.42 ± 0.99	0.001

EEL = external elastica lamina
* Mean ± standard deviation

paque stent material for reliable control of the implantation result in routine clinical practice.

Although no adjunctive anticoagulation nor antiplatelet drugs were given after successful deployment of the stents, none of the metallic stents occluded. In contrast, three of the eight successfully deployed PET stents showed an organized thrombotic occlusion at histopathology, confirming our earlier suggestion that PET material may be thrombogenic [7].

At 6 weeks, the intrastent diameter of the metallic stents was virtually unaltered on angiography when compared with immediately poststenting, but the PET material induced a diameter reduction of 30%, correlating to histomorphometry, where in the PET-stented vessel segments a diameter stenosis of 40% was measured vs only 9% in the metallic stents. This impressive difference in the degree of neointimal proliferation was noted in the presence of a minor but similar degree of vessel-wall injury, that is, disruption of the internal elastic membrane.

Murphy et al. [6] implanted 11 self-expanding PET stents in porcine coronary arteries and found all occluded after 4–6 weeks, along with a chronic foreign-body inflammatory response with lymphocytes, eosinophils, and giant cells surrounding the stent filaments, with a marked neointimal proliferative response in the center of the vessel. Van der Giessen et al. [8] implanted five self-expanding stents in porcine peripheral arteries but, at 4 weeks follow-up, he found only 16% additional vessel narrowing when compared with immediately poststenting. As in our study, the covering of his stent filaments consisted of smooth muscle cells in a collagenous matrix. Most probably these striking differences in the results of the three studies testing PET as stent material are related to differences in the composition or contamination of the polymer used. Furthermore, since coronary arteries consist mainly of smooth muscle cells, whereas elastic tissue is predominant in the larger peripheral vessels, it has been suggested that the coronary arterial reaction to injury is more intense than that of peripheral arteries.

In conclusion, compared with Wallstents, self-expanding PET polymer stents exert less expansile force resulting in suboptimal deployment and even displacement during the implantation procedure. Furthermore, thrombogenicity of PET stents is not reduced, and most importantly, the PET material used for our stents consistently induced a much higher degree of neointimal proliferation. These undesired properties render self-expanding PET stents unsuitable for human investigation.

Acknowledgments: The authors wish to thank Tony Stassen for excellent technical assistance and Joke Tack for excellent secretarial assistance in preparing the manuscript.

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EXHIBIT A

ANTONIOS G. MIKOS

Curriculum Vitae

Education

Ph.D. (Ch.E.), Purdue University, 1988
M.S.Ch.E., Purdue University, 1985
Dipl.Ch.E., Aristotle University of Thessaloniki, Greece, 1983

Professional Experience

2008-	Louis Calder Professor of Bioengineering and Chemical and Biomolecular Engineering, Departments of Bioengineering and Chemical and Biomolecular Engineering, Rice University
1999-2008	John W. Cox Professor of Bioengineering and Chemical and Biomolecular Engineering, Departments of Bioengineering and Chemical and Biomolecular Engineering, Rice University
1999-	Director of John W. Cox Laboratory for Biomedical Engineering, Rice University
1999-	Director of Center for Excellence in Tissue Engineering, Rice University
2002-	Adjunct Professor, Department of Oral and Maxillofacial Surgery, University of Texas Health Science Center at Houston
1996-1999	Associate Professor of Bioengineering and Chemical Engineering, Departments of Bioengineering and Chemical Engineering, Rice University
1998	Visiting Associate Professor of Pharmaceutics and Pharmaceutical Chemistry, Center for Controlled Chemical Delivery, University of Utah
1998	Visiting Associate Professor of Biology and Pathology, Departments of Biology and Pathology, Case Western Reserve University
1992-1996	T.N. Law Assistant Professor of Chemical Engineering and Bioengineering, Department of Chemical Engineering, Rice University
1990-1991	Research Associate, Department of Chemical Engineering, Massachusetts Institute of Technology, and Department of Surgery, The Children's Hospital of Boston, Harvard Medical School
1989	Research Associate, Management of Chemistry Laboratories, Greek Navy
1988	Research Associate, Chemical Process Engineering Research Institute, Thessaloniki, Greece
1983-1988	Research Assistant, Purdue University
1982 (Sum.)	Research Assistant, Center for Chemical Research, Bratislava, Czechoslovakia

Awards

2008	Outstanding Chemical Engineer Award, Purdue University
2008	Distinguished Scientist Award, Houston Society for Engineering in Medicine and Biology

2007	Alpha Chi Sigma Award for Chemical Engineering Research, American Institute of Chemical Engineers
2007	Robert A. Pritzker Distinguished Lecturer Award, Biomedical Engineering Society
2007	Edith and Peter O'Donnell Award in Engineering, The Academy of Medicine, Engineering and Science of Texas
2007	Oral Abstract Scientific Presentation Award, Annual Meeting of the American Association of Oral and Maxillofacial Surgeons
2005	Marshall R. Urist Award for Excellence in Tissue Regeneration Research, Orthopaedic Research Society
2003	Huygens Lecturer Award, Netherlands Organization for Scientific Research
2003	Innovation Award, Advanced Materials Research Center, Singapore
2001	Clemson Award for Contributions to the Literature, Society For Biomaterials
2000	Best Poster Award, Materials Research Society Fall Meeting
2000	Phoenix Pharmazie-Wissenschaftspreis (Pharmaceutical Science Award)
2000	Fellow, International Union of Societies for Biomaterials Science and Engineering
2000	Hershel M. Rich Invention Award, Rice University
1999	Fellow, American Institute for Medical and Biological Engineering
1998	Young Investigator Research Achievement Award, Controlled Release Society
1997	Hershel M. Rich Invention Award, Rice University
1996	Outstanding Young Investigator Award, Materials Research Society
1996	FIRST Award, National Institutes of Health
1995	Hershel M. Rich Invention Award, Rice University
1994	Whitaker Young Investigator Award, Biomedical Engineering Society
1994	Johnson & Johnson Medical Outstanding Young Scientist Award, Houston Society for Engineering in Medicine and Biology
1991	Victor K. LaMer Award for Outstanding Ph.D. Thesis, American Chemical Society
1988, 1985	Sigma Xi Student Research Competition Award
1983	Technical Chamber of Greece Award

Endowed/Honorary Lectureships

2008	Keynote Lecturer, International Conference on Research Strategy of Tissue Engineering, Jinan, China
2008	Keynote Lecturer, Tenth International Symposium on Biomineralization, Lianyungang, China
2008	Keynote Lecturer, Annual Symposium of Baylor College of Medicine Medical Scientist Training Program, Galveston, Texas
2008	Keynote Lecturer, World Biomaterials Congress, Amsterdam, The Netherlands
2008	Keynote Lecturer, Tenth Anniversary Celebration of Korean Tissue Engineering and Regenerative Medicine Society Meeting, Seoul, Korea
2008	Robert A. Pritzker Distinguished Lecturer, Illinois Institute of Technology, Chicago, Illinois

2007	Keynote Lecturer, Annual Meeting of the Dutch Society for Biomaterials and Tissue Engineering, Lunteren, The Netherlands
2007	Centenary Seminar Series Lecturer, Imperial College, London, England
2007	James Gibb Johnson Distinguished Visiting Lecturer, University of Tennessee Health Science Center, Memphis, Tennessee
2007	Keynote Lecturer, Third Marie Curie Cutting Edge InVENTS Conference, Madeira, Portugal
2006	Keynote Lecturer, International Conference on Biomedical and Pharmaceutical Engineering, Singapore
2006	Keynote Lecturer, Annual Meeting of Japanese Society for Tissue Engineering, Kyoto, Japan
2006	Keynote Lecturer, Symposium on Nanomedicine and Tissue Engineering in Memory of Professor C.J. Lee, National Tsing Hua University, Hsinchu, Taiwan
2006	Koret Foundation Lecturer, University of California Davis, Sacramento, California
2006	Keynote Lecturer, First Marie Curie Cutting Edge InVENTS Conference, Madeira, Portugal
2006	Keynote Lecturer, Rebuilding Humans: The Seattle Tissue Engineering Initiative Symposium, Seattle, Washington
2005	Keynote Lecturer, Annual Meeting of Tissue Engineering Society International, Shanghai, China
2005	Keynote Lecturer, International Conference on Materials for Advanced Technologies, Singapore
2004	Procter and Gamble Lecturer, Iowa State University, Ames, Iowa
2004	Roger Malkin Distinguished Lecturer, Mississippi State University, Mississippi State, Mississippi
2003	Keynote Lecturer, First International Conference on Epithelial Technologies and Tissue Engineering, Singapore
2002	Keynote Lecturer, Annual Meeting of the Dutch Society for Biomaterials and Tissue Engineering, Lunteren, The Netherlands
2000	Keynote Lecturer, Research Council Meeting of Japan Society of Plastic and Reconstructive Surgery, Nagoya, Japan
2000	Keynote Lecturer, Annual Meeting of Japan Society of Drug Delivery System, Akita, Japan
1999	Distinguished Lecturer, University of Maryland, College Park, Maryland
1999	Keynote Lecturer, Academy of Dental Materials Annual Meeting, Tempe, Arizona
1998	Keynote Lecturer, Bionic Design Workshop, Tsukuba, Japan
1995	Keynote Lecturer, First International Congress on Cellular Therapy & Tissue Engineering, Washington, D.C.

Honors

2008	Chair, Third Aegean Conference on Tissue Engineering, Rhodes, Greece
2008	Invited Lecturer, A Celebration of Excellence in Scientific and Engineering Achievement on the Occasion of Nicholas Peppas' 60th Birthday, Austin, Texas

2008	Invited Lecturer, Conference on Regenerative Endodontics, Nova Southeastern University, Fort Lauderdale, Florida
2007	Invited Lecturer, Integrated Research Team Meeting on Nanotechnology Solutions for Long-Term Implantable Devices, Houston, Texas
2007	Invited Lecturer, International Bone Fluid Flow Workshop, New York, New York
2007	Invited Lecturer, Symposium on Musculoskeletal Biology, Stem Cells and Clinical Translation: A Celebration of Arnold Caplan's 65th Birthday, Cleveland, Ohio
2006	Invited Lecturer, International Collaborative Symposium on Stem Cell Research, Seoul, Korea
2006	Invited Lecturer, US-Japan Joint Topical Conference on Medical Engineering, Drug Delivery Systems and Therapeutic Systems, Annual AIChE Meeting, San Francisco, California
2006	Chair, Annual Meeting and Exposition of Controlled Release Society, Vienna, Austria
2006	Invited Lecturer, Conference Celebrating Thirty Years of Robert Langer's Science, Cambridge, Massachusetts
2006	Author of One of Twenty-Five Best Papers Published in Biomaterials 1980-2004
2006	Research Advisor of Sallyport Award, Association of Rice Alumni
2006	Research Advisor of Distinguished Senior Award, Rice Engineering Alumni Association
2006	Invited Lecturer, Regenerate World Congress on Tissue Engineering and Regenerative Medicine, Pittsburgh, Pennsylvania
2006	Invited Lecturer, Scientific Conference of Society for Physical Regulation in Biology and Medicine, Cancun, Mexico
2006	Invited Lecturer, International Cartilage Repair Society Symposium, San Diego, California
2005	Invited Lecturer, Pharmaceutical Sciences Symposium Honoring the Career of Professor Joseph R. Robinson, University of Wisconsin, Madison, Wisconsin
2005	Invited Lecturer, Texas/United Kingdom Symposium on Medicine and Medical Devices, Rice University
2005	Invited Lecturer, International Bone Fluid Flow Workshop, New York, New York
2005	Research Advisor of First Prize in Keck Center Annual Research Conference Poster Contest, Gulf Coast Consortia
2005	Invited Lecturer, Symposium on New Trends in Biomaterials-Tissue Engineering, National University of Singapore, Singapore
2005	Chair, Second Aegean Conference on Tissue Engineering, Crete, Greece
2005	Research Advisor of Graduate Student Award for Outstanding Research, Society For Biomaterials
2005	Invited Lecturer, Tissue Engineering: The Next Generation Workshop, Cambridge, Massachusetts
2005	Invited Lecturer, International Symposium on Recent Advances in Drug Delivery Systems, Salt Lake City, Utah
2004	Invited Lecturer, Fall Meeting of the Materials Research Society, Boston, Massachusetts

2004	Invited Lecturer, Southeastern Regional Meeting of the American Chemical Society, Research Triangle Park, North Carolina
2004	Invited Lecturer, Annual Meeting of the American Institute of Chemical Engineers, Austin, Texas
2004	Research Advisor of Ralph Budd Award for Best Engineering Ph.D. Thesis, Rice University
2004	Research Advisor of James S. Waters Creativity Award, Rice University
2004	Invited Lecturer, First Biennial Symposium on Tissue Engineering and Regeneration, University of Michigan, Ann Arbor
2004	Invited Lecturer, European Symposium on Controlled Drug Delivery, Noordwijk aan Zee, The Netherlands
2004	Invited Lecturer, United Kingdom/Texas Symposium on Tissue Engineering and Regenerative Medicine, Imperial College, London, England
2004	Invited Lecturer, National American Chemical Society Meeting, Anaheim, California
2004	Invited Lecturer, Annual Meeting of the International Association for Dental Research, Honolulu, Hawaii
2003	Invited Lecturer, American Institute of Chemical Engineers Annual Meeting, San Francisco, California
2003	Invited Lecturer, Symposium Tissue Engineering, Netherlands Technology Foundation, Ede, The Netherlands
2003	Invited Lecturer, International Bone Fluid Flow Workshop, Cleveland, Ohio
2003-2007	Member, National Institute of Dental and Craniofacial Research Special Grants Review Committee
2003	Chairperson, Center for Scientific Review Special Emphasis Panel on Advanced Biomaterials, National Institutes of Health
2003	Invited Lecturer, Annual Meeting of Orthopaedic Research Society, New Orleans, Louisiana
2002	Invited Lecturer, Polymers in Medicine and Biology: 2002, Rohnert Park, California
2002	Chair, Engineering in Medicine and Biology Society - Biomedical Engineering Society Joint Conference, Houston, Texas
2002	Invited Lecturer, International Conference on Bone Morphogenetic Proteins, Sacramento, California
2002	Invited Lecturer, Smith & Nephew International Symposium on Translating Tissue Engineering into Products, Atlanta, Georgia
2002	Invited Lecturer, Annual Meeting of the Controlled Release Society, Seoul, Korea
2002	Chair, Aegean Conference on Tissue Engineering Science, Myconos, Greece
2002	Research Advisor of Ralph Budd Award for Best Engineering Ph.D. Thesis, Rice University
2002	Research Advisor of Graduate Student Award for Outstanding Research, Society For Biomaterials
2002	Research Advisor of Tissue Engineering Special Interest Group Student Award, Society For Biomaterials
2002	Invited Lecturer, Edward C. Hinds Symposium on Contemporary Oral and Maxillofacial Surgery, Houston, Texas

2002	Invited Lecturer, Annual Meeting of the Society For Biomaterials, Tampa, Florida
2002	Invited Lecturer, Annual Meeting of the American Association of Anatomists, New Orleans, Louisiana
2002	Invited Lecturer, Engineering Tissue Growth International Conference and Exposition, Pittsburgh, Pennsylvania
2002	Invited Lecturer, Biomaterials - The Next Frontiers Conference, University of Delaware, Newark, Delaware
2002	Invited Lecturer, Foundation for Research and Technology Hellas Conference, Metsovo, Greece
2002	Invited Lecturer, American Association of Pharmaceutical Scientists Workshop, Arlington, Virginia
2001	Invited Lecturer, Annual Conference on Regenerative Medicine: Rebuilding the Human Body, Washington, D.C.
2001	Invited Panelist, Bioengineering Consortium Symposium on Regenerative Medicine: Growing Tissues and Organs, National Institutes of Health
2001	Research Advisor of Best Poster Award, Baylor College of Medicine M.D./Ph.D. Symposium
2001	Research Advisor of James S. Waters Creativity Award, Rice University
2001	Invited Lecturer, Human Genome Odyssey Conference: The Science, Business, Law and Ethics of Engineering Human Life, Akron, Ohio
2001	Invited Lecturer, Engineering Tissue Growth International Conference and Exposition, Pittsburgh, Pennsylvania
2000	Chair, Materials Research Society Fall Meeting, Boston, Massachusetts
2000	Invited Lecturer, International Symposium on Tissue Engineering for Therapeutic Use, Tsukuba, Japan
2000	Research Advisor of Best Paper Award, Texas Medical Scientist Training Program Conference
2000	Invited Lecturer, Council for the Advancement of Science Writing Annual Briefing, Houston, Texas
2000	Invited Lecturer, Surfaces in Biomaterials, Scottsdale, Arizona
2000	Invited Lecturer, International Symposium on Biomaterials and Drug Delivery Systems, Cheju Island, Korea
2000	Research Advisor of Graduate/Postdoc Award on Innovative Aspects of Controlled Drug Release, Controlled Release Society-Capsugel
2000	Invited Lecturer, International Conference on Bone Morphogenetic Proteins, Lake Tahoe, California
2000	Invited Lecturer, Croucher Advanced Study Institute on Engineering of Musculoskeletal Tissues, Kowloon, Hong Kong
2000	Invited Lecturer, European Symposium on Controlled Drug Delivery, Noordwijk aan Zee, The Netherlands
2000	Invited Lecturer, Translation of Biomaterials Research into Biotechnology Symposium, University of Chicago, Chicago, Illinois
2000	Invited Lecturer, Annual Meeting of Orthopaedic Research Society and American Academy of Orthopaedic Surgeons, Orlando, Florida
2000	Alessandro Codivilla Lecturer, Association for the Study and Application of the Methods of Ilizarov Annual Scientific Meeting, Orlando, Florida

2000	Invited Lecturer, Research Initiatives Conference in Vascular Disease, Bethesda, Maryland
1999	Invited Lecturer, BioValley Tissue Engineering Symposium, Freiburg, Germany
1999	Invited Lecturer, Asia-Pacific Conference on Medical and Biological Engineering, Seoul, Korea
1999	Invited Lecturer, Gordon Research Conference on Tissue Engineering, Biomaterials, and Biocompatibility, Plymouth, New Hampshire
1999	Member, Biomimetics and Tissue Engineering in the Restoration of Orofacial Tissues Study Section, National Institutes of Health
1999	Invited Lecturer, Congress on In Vitro Biology, New Orleans, Louisiana
1999	Member, Dental, Oral and Craniofacial Health Technology Forum, National Institute of Dental and Craniofacial Research/Food and Drug Administration
1999	Invited Lecturer, International Workshop on Calcified Tissues, Eilat, Israel
1998	Research Advisor of Graduate Student Award for Outstanding Research, Society For Biomaterials
1998	Research Advisor of Excellence in Science Dissertation Award for Best Ph.D. Thesis, Sigma Xi
1998	Research Advisor of Graduate Student Award for Best Paper, Southern Biomedical Engineering Conference
1998	Member, Functional Biomaterials Panel, Bioengineering Consortium Symposium, National Institutes of Health
1998	Invited Lecturer, Association of Bone and Joint Surgeons Orthopaedic Tissue Engineering Workshop, Tampa, Florida
1998	Invited Lecturer, International Business Communications Industry Symposium on Advancements in Tissue Engineering, Boston, Massachusetts
1997-2000	Ad Hoc Member, Oral Biology and Medicine Study Section, National Institutes of Health
1997	Invited Lecturer, Workshop on Tissue Based Biosensors, Defense Advanced Research Projects Agency, Ashburn, Virginia
1997	Invited Lecturer, Annual Symposium of Macromolecular Science and Engineering Center, The University of Michigan, Ann Arbor, Michigan
1997	Invited Lecturer, Medical Textiles Conference, Clemson University, Clemson, South Carolina
1997	Invited Lecturer, Portland Bone Symposium, Portland, Oregon
1997	Invited Lecturer, First Smith & Nephew International Symposium on Advances in Tissue Engineering and Biomaterials, York, England
1997	Research Advisor of Graduate Student Award for Outstanding Research, Society For Biomaterials
1997	Research Advisor of Selected Excellence Paper, Society For Biomaterials
1997	Research Advisor of Ralph Budd Award for Best Engineering Ph.D. Thesis, Rice University
1997	Research Advisor of Ph.D. Thesis Award, Sigma Xi
1997	Research Advisor of James S. Waters Creativity Award, Rice University
1997	Invited Lecturer, International Symposium on Recent Advances in Drug Delivery Systems, Salt Lake City, Utah

1997	Research Advisor of Poster Award, Houston Society for Engineering in Medicine and Biology
1996-1998	Member, Clinical Sciences Special Emphasis Panel, Muscular, Skeletal, and Dental Initial Review Group, National Institutes of Health
1996	Research Advisor of Excellence in Bioengineering, Dr. William B. Walsh Award, Advanced Tissue Sciences
1996	Research Advisor of James S. Waters Creativity Award, Rice University
1996	Research Advisor of Honorable Mention, Poster Award, Houston Society for Engineering in Medicine and Biology
1996	Member, Workshop on Biomimetics, Tissue Engineering, and Biomaterials, National Institute of Dental Research
1996	Invited Lecturer, International Symposium on Endocrine Cell Transplantation and Genetic Engineering, Giessen, Germany
1995	Invited Lecturer, Taniguchi Conference on the Tissue Engineering with the Use of Biomedical Polymers, Kyoto, Japan
1995	Invited Lecturer, International Business Communications Conference on Tissue Engineering and Repair, Washington, D.C.
1995	Research Advisor of Distinguished Contribution, BFGoodrich Collegiate Inventors Program
1995	Research Advisor of Best Undergraduate Polymer Research, POLYED Award, American Chemical Society
1995	Founding Member, Tissue Engineering Society
1995	Invited Lecturer, American Society for Artificial Internal Organs Conference, Chicago, Illinois
1995	Ad Hoc Member, Biomedical Research Technology Review Committee, National Institutes of Health
1995	Invited Lecturer, American Association for the Advancement of Science Meeting, Atlanta, Georgia
1995	Research Advisor of Best Poster, Intermedics Award, Houston Society for Engineering in Medicine and Biology
1994	Invited Lecturer, Surfaces in Biomaterials, Scottsdale, Arizona
1994	Invited Lecturer, World Congress of Biomechanics, Amsterdam, The Netherlands
1994	Invited Lecturer, International ITV Conference on Biomaterials, Denkendorf, Germany
1993	Research Advisor of Best Undergraduate Polymer Research, POLYED Award, American Chemical Society
1993	Research Advisor of James S. Waters Creativity Award, Rice University
1993	Invited Lecturer, Monte Verità Conference, Ascona, Switzerland
1992	Invited Lecturer, Jerusalem Conference on Pharmaceutical Sciences and Clinical Pharmacology, Jerusalem, Israel
1992	Invited Lecturer, Hispanic and Hispanic-Portuguese Congress on Biotechnology, Santiago de Compostela, Spain

Editorial Boards

Tissue Engineering Part A (1995-), **Editor-in-Chief** (1995-)

Tissue Engineering Part B: Reviews (2008-), **Editor-in-Chief** (2008-)
Tissue Engineering Part C: Methods (2008-), **Editor-in-Chief** (2008-)
Advanced Drug Delivery Reviews (2004-)
Biomaterials (1994-), Special Issues Editor (1998-2007), Guest Editor of Two Special Issues on Tissue Engineering (1996)
Cell Transplantation (1994-)
Electronic Journal of Biotechnology (1997-)
Journal of Biomaterials Science, Polymer Edition (1996-), Guest Editor of Three Special Issues on Cells at Interfaces (1998)
Journal of Biomedical Materials Research (1996-)
Journal of Biomedical Materials Research, Applied Biomaterials (2003-)
Journal of Controlled Release (2000-)
Journal of Drug Targeting (1999-2003)
Journal of Tissue Engineering and Regenerative Medicine (2007-)
Annual Review of Biomedical Engineering, Volume 5 (2003)
Tissue Engineering Intelligence Unit, R.G. Landes Company and Academic Press (1995-)
Tissue Engineering Series, Birkhäuser/Springer (1996-)

Academic Advisory Boards

Carnegie Mellon University, Institute for Complex Engineered Systems (2008-)
Radboud University Nijmegen, Nijmegen Centre for Molecular Life Sciences (2005)
The Cleveland Clinic Foundation, Clinical Tissue Engineering Center (2004-)
National Tissue Engineering Center (2003-)
University of Michigan, Tissue Engineering and Regeneration Training Program (2002-)
University of Utah, Department of Bioengineering (1999)
Purdue University, Tissue Engineering (1998-2002)
Baylor College of Medicine/Rice University, Medical Scientist Training Program
Faculty Operating Committee Member (1995-)
Executive Committee Member (2006-)
The University of Texas Health Science Center at Houston, Dental Branch (1993-)

Scientific Advisory Committees

International Conference on Materials for Advanced Technologies, Singapore (2009)
Annual Conference of Tissue Engineering and Regenerative Medicine International Society – Asia Pacific Region, Taipei, Taiwan (2008)
International Conference on Smart Materials, Structures and Systems, Acireale, Sicily, Italy (2008)
International Conference on Advances in Bioresorbable Biomaterials for Tissue Engineering, Singapore (2008)
European Symposium on Controlled Drug Delivery, Noordwijk Aan Zee, The Netherlands (2006-)
First Marie Curie Cutting Edge InVENTS Conference on New Developments on Polymers for Tissue Engineering, Replacement and Regeneration, Madeira, Portugal (2006)
Annual Meeting of Society For Biomaterials, Pittsburgh, Pennsylvania (2006)

Aegean Conferences (2005-)
Annual Meeting of Tissue Engineering Society International, Shanghai, China (2005)
Summer School on Emerging Technologies in Biomedicine, University of Patras, Greece (2005-)
Marcus Evans Conferences (2003-)
International Conference on Materials for Advanced Technologies, Singapore (2003)
Engineering Tissue Growth International Conference and Exposition, Pittsburgh, Pennsylvania (2003)
Cell-Based Therapies and Tissue Engineering Short Course, Case Western Reserve University, Cleveland, Ohio (2002-)
NATO Advanced Study Institute on Polymer Based Systems on Tissue Engineering, Replacement and Regeneration, Alvor, Portugal (2001)
International Symposium on Frontiers in Biomedical Polymers Including Polymer Therapeutics, Shiga, Japan (1999)

Professional Societies

American Institute for Medical and Biological Engineering (AIMBE)
American Institute of Chemical Engineers (AIChE)
Chair of Area 15d/e Engineering Fundamentals in Life Science (1997-99), Vice Chair (1995-97); Chair of Area 8b Biomaterials (1994-96), Vice-Chair (1992-94)
Association for Research in Vision and Ophthalmology (ARVO)
Society For Biomaterials (SFB)
Chair of Hybrid Artificial Organs Special Interest Group (1993-95); Member-at-Large (2004-2005); Delegate in International Union of Societies for Biomaterials Science and Engineering (2004-); Secretary/Treasurer-Elect (2007-)
Biomedical Engineering Society (BMES)
Controlled Release Society (CRS)
Global Network Team (1994-96); Chair of Workshop Committee (1996-98)
Materials Research Society (MRS)
External Affairs Committee (1995-2003); Chair of 2000 Fall MRS Meeting
Tissue Engineering and Regenerative Medicine International Society (TERMIS)
Continental Chair-Elect of TERMIS-North America (2005-)
Tissue Engineering Society International (TESi)
Founding Member; Clerk/Secretary (1996-1998); Vice-President (1998-2000); Member Governor (2003-2005)
Orthopaedic Research Society
Chair of Biomaterials Topic Committee (2005-2006)
International Association for Dental Research (IADR)
Cell Transplant Society
American Chemical Society (ACS)
American Association for the Advancement of Science (AAAS)
The New York Academy of Sciences
Houston Society for Engineering in Medicine and Biology (HSEMB)
Steering Committee (1995-97)
Technical Chamber of Greece
Greek Chemical Engineers Association

Greek Polymer Society
Sigma Xi

Registered Professional Engineer

Technical Chamber of Greece (1983-)

Books

1. A.G. Mikos, R. Murphy, H. Bernstein, and N.A. Peppas, "Biomaterials for Drug and Cell Delivery," MRS Symposium Proceedings, Vol. 331, Materials Research Society, Pittsburgh, 1994.
2. A.G. Mikos, K.W. Leong, M.J. Yaszemski, J.A. Tamada, and M.L. Radomsky, "Polymers in Medicine and Pharmacy," MRS Symposium Proceedings, Vol. 394, Materials Research Society, Pittsburgh, 1995.
3. N.A. Peppas, D.J. Mooney, A.G. Mikos, and L. Brannon-Peppas, "Biomaterials, Carriers for Drug Delivery, and Scaffolds for Tissue Engineering," American Institute of Chemical Engineers, New York, 1997.
4. R.C. Thomson, D.J. Mooney, K.E. Healy, Y. Ikada, and A.G. Mikos, "Biomaterials Regulating Cell Function and Tissue Development," MRS Symposium Proceedings, Vol. 530, Materials Research Society, Pittsburgh, 1998.
5. C.W. Patrick, Jr., A.G. Mikos, and L.V. McIntire, "Frontiers in Tissue Engineering," Elsevier Science, New York, 1998.
6. D.L. Wise, A. Klibanov, R. Langer, A.G. Mikos, L. Brannon-Peppas, N.A. Peppas, D.J. Trantolo, G.E. Wnek, and M.J. Yaszemski, "Handbook of Pharmaceutical Controlled Release Technology," Marcel Dekker, New York, 2000.
7. A.G. Mikos, "NWO | Huygens Lecture 2003: Tissue Engineering," Netherlands Organization for Scientific Research, The Hague, 2003.
8. F. Bronner, M.C. Farach-Carson, and A.G. Mikos, "Engineering of Functional Skeletal Tissues," Topics in Bone Biology, Vol. 3, Springer-Verlag, London, 2007.
9. J.P. Fisher, A.G. Mikos, and J.D. Bronzino, "Tissue Engineering," CRC Press, Boca Raton, 2007.
10. J.J. Mao, G. Vunjak-Novakovic, A.G. Mikos, and A. Atala, "Translational Approaches in Tissue Engineering and Regenerative Medicine," Artech House, Norwood, 2008.
11. J.S. Temenoff and A.G. Mikos, "Biomaterials: The Intersection of Biology and Materials Science," Pearson Prentice Hall, Upper Saddle River, 2008.

Journal Special Issues and Book Sections

1. A.G. Mikos, "Polymer Scaffolding and Hard Tissue Engineering," *Biomaterials,* Special Issue I on Tissue Engineering, Vol. 17, No. 2, 1996.
2. A.G. Mikos, "Tissue Technologies and Soft Tissue Engineering," *Biomaterials,* Special Issue II on Tissue Engineering, Vol. 17, No. 3, 1996.
3. T.A. Horbett, A.G. Mikos, and D.J. Mooney, *J. Biomater. Sci., Polym. Ed.,* Special Issue I on Cells at Interfaces, Vol. 9, No. 8, 1998.

4. T.A. Horbett, A.G. Mikos, and D.J. Mooney, *J. Biomater. Sci., Polym. Ed.,* Special Issue II on Cells at Interfaces, Vol. 9, No. 11, 1998.
5. T.A. Horbett, A.G. Mikos, and D.J. Mooney, *J. Biomater. Sci., Polym. Ed.,* Special Issue III on Cells at Interfaces, Vol. 9, No. 12, 1998.
6. T.A. Horbett, A.G. Mikos, and D.J. Mooney, *J. Biomater. Sci., Polym. Ed.,* Special Issue IV on Cells at Interfaces, Vol. 10, No. 2, 1999.
7. A.G. Mikos, "Section Five: Active Implants" (Four Chapters), in *Handbook of Biomaterials Evaluation,* 2nd ed., A.F. von Recum, Ed., Taylor & Francis, Philadelphia, 1999, pp. 383-460.
8. Y.H. Bae and A.G. Mikos, *Adv. Drug Deliv. Rev.,* Special Issue on Cells as Drug Delivery Platforms, Vol. 42, Nos. 1-2, 2000.
9. D.J. Mooney and A.G. Mikos, *J. Drug Target.,* Special Issue on Tissue Engineering, Vol. 9, No. 6, 2001.
10. J.P. Fisher and A.G. Mikos, "Tissue Engineering" (Thirty-Three Chapters), in *Tissue Engineering and Artificial Organs,* The Biomedical Engineering Handbook, Vol. 3, 3rd Ed., J.D. Bronzino, Ed., CRC Press, Boca Raton, 2006, pp. 30–1-62–19.
11. W.T. Godbey and A.G. Mikos, *Adv. Drug Deliv. Rev.,* Special Issue on Gene Delivery for Tissue Engineering, Vol. 58, No. 4, 2006.
12. A. Domb and A.G. Mikos, *Adv. Drug Deliv. Rev.,* Special Issue on Matrices and Scaffolds for Drug Delivery in Tissue Engineering, Vol. 59, Nos. 4-5, 2007.
13. E. Cosgriff-Hernandez and A.G. Mikos, *Pharm. Res.,* Special Issue on New Biomaterials as Scaffolds for Tissue Engineering, Vol. 25, No. 10, 2008.

Publications

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2. A.G. Mikos, C.G. Takoudis, and N.A. Peppas, "Reaction Engineering Aspects of Suspension Polymerization," *J. Appl. Polym. Sci., 31,* 2647-2659 (1986).
3. A.G. Mikos and N.A. Peppas, "Systems for Controlled Release of Drugs. V. Bioadhesive Systems," *S.T.P. Pharma, 2,* 705-716 (1986).
4. N.A. Peppas, M.L. Brannon, R.S. Harland, J. Klier, S.R. Lustig, and A.G. Mikos, "Influence of the Polymer Structure on Controlled Solute Release," *Bull. Techn. Gattefossé, 79,* 7-17 (1986).
5. A.G. Mikos, C.G. Takoudis, and N.A. Peppas, "Evidence of Unequal Vinyl Group Reactivity in Copolymerization/Crosslinking Reactions of Mono- and Divinyl Comonomers," *Polymer, 28,* 998-1004 (1987).
6. A.G. Mikos and N.A. Peppas, "A model for Prediction of the Structural Characteristics of EGDMA-Crosslinked PHEMA Microparticles Produced by Suspension Copolymerization/ Crosslinking," *J. Controlled Release, 5,* 53-62 (1987).
7. A.G. Mikos and N.A. Peppas, "Prediction of Feed Comonomer and Solvent Composition for Monomer-Free Polymer Production," *Biomaterials, 8,* 404-406 (1987).
8. A.G. Mikos and N.A. Peppas, "Flory Interaction Parameter χ for Hydrophilic Copolymers with Water," *Biomaterials, 9,* 419-423 (1988).
9. A.G. Mikos and N.A. Peppas, "Healing and Fracture at the Interface between two Gels," *Europhys. Lett., 6,* 403-406 (1988).

10. A.G. Mikos and N.A. Peppas, "Polymer Chain Entanglements and Brittle Fracture," *J. Chem. Phys., 88,* 1337-1342 (1988).
11. A.G. Mikos and N.A. Peppas, "Polymer Chain Entanglements and Brittle Fracture. II. Autohesion of Linear Polymers," *Polymer, 30,* 84-91 (1989).
12. A.G. Mikos and N.A. Peppas, "Polymer Chain Entanglements and Brittle Fracture. III. Critical Fracture Strength of Macromolecular Materials," *J. Mater. Sci. Lett., 8,* 833-834 (1989).
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14. A.G. Mikos and N.A. Peppas, "Measurement of the Surface Tension of Mucin Solutions," *Int. J. Pharm., 53,* 1-5 (1989).
15. N.A. Peppas and A.G. Mikos, "Experimental Methods for Determination of Bioadhesive Bond Strength of Polymers with Mucus," *S.T.P. Pharma, 5,* 187-191 (1989).
16. A.B. Scranton, A.G. Mikos, L.C. Scranton, and N.A. Peppas, "The Physical Mechanism for the Production of Hydrophilic Polymer Microparticles from Aqueous Suspensions," *J. Appl. Polym. Sci., 40,* 997-1004 (1990).
17. A.G. Mikos and N.A. Peppas, "Bioadhesive Analysis of Controlled-Release Systems. IV. An Experimental Method for Testing the Adhesion of Microparticles with Mucus," *J. Controlled Release, 12,* 31-37 (1990).
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19. A.G. Mikos and C. Kiparissides, "Skin Formation in Heterogeneous Polymerization Reactions," *J. Membrane Sci., 59,* 205-217 (1991).
20. A.G. Mikos, E. Mathiowitz, R. Langer, and N.A. Peppas, "Interaction of Polymer Microspheres with Mucin Gels as a Means of Characterizing Polymer Retention on Mucus," *J. Colloid Interface Sci., 143,* 366-373 (1991).
21. L.E. Freed, J.C. Marquis, A. Nohria, J. Emmanual, A.G. Mikos, and R. Langer, "Neocartilage Formation *In Vitro* and *In Vivo* Using Cells Cultured on Synthetic Biodegradable Polymers," *J. Biomed. Mater. Res., 27,* 11-23 (1993).
22. A.G. Mikos, Y. Bao, L.G. Cima, D.E. Ingber, J.P. Vacanti, and R. Langer, "Preparation of Poly(Glycolic Acid) Bonded Fiber Structures for Cell Attachment and Transplantation," *J. Biomed. Mater. Res., 27,* 183-189 (1993).
23. H.L. Wald, G. Sarakinos, M.D. Lyman, A.G. Mikos, J.P. Vacanti, and R. Langer, "Cell Seeding in Porous Transplantation Devices," *Biomaterials, 14,* 270-278 (1993).
24. A.G. Mikos, G. Sarakinos, S.M. Leite, J.P. Vacanti, and R. Langer, "Laminated Three-Dimensional Biodegradable Foams for Use in Tissue Engineering," *Biomaterials, 14,* 323-330 (1993).
25. A.G. Mikos and N.A. Peppas, "Bioadhesive Phenomena in Controlled Release Systems," *Pharmakeftiki, 6,* 1-10 (1993).
26. A.G. Mikos, G. Sarakinos, M.D. Lyman, D.E. Ingber, J.P. Vacanti, and R. Langer, "Prevascularization of Porous Biodegradable Polymers," *Biotechnol. Bioeng., 42,* 716-723 (1993).
27. A.G. Mikos, M.D. Lyman, L.E. Freed, and R. Langer, "Wetting of Poly(L-Lactic Acid) and Poly(DL-Lactic-co-Glycolic Acid) Foams for Tissue Culture," *Biomaterials, 15,* 55-58 (1994).

28. A.G. Mikos, A.J. Thorsen, L.A. Czerwonka, Y. Bao, R. Langer, D.N. Winslow, and J.P. Vacanti, "Preparation and Characterization of Poly(L-Lactic Acid) Foams," *Polymer, 35,* 1068-1077 (1994).
29. A.G. Mikos, M.G. Papadaki, S. Kouvroukoglou, S.L. Ishaug, and R.C. Thomson, "Islet Transplantation to Create a Bioartificial Pancreas," *Biotechnol. Bioeng., 43,* 673-677 (1994).
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31. S.L. Ishaug, M.J. Yaszemski, R. Bizios, and A.G. Mikos, "Osteoblast Function on Synthetic Biodegradable Polymers," *J. Biomed. Mater. Res., 28,* 1445-1453 (1994).
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37. A.D. Ouellette, K.K. Wu, and A.G. Mikos, "Cardiovascular Gene Transfer," *Tissue Eng., 1,* 311-322 (1995).
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39. M.J. Yaszemski, R.G. Payne, W.C. Hayes, R. Langer, and A.G. Mikos, "The Evolution of Bone Transplantation: Molecular, Cellular, and Tissue Strategies to Engineer Human Bone," *Biomaterials, 17,* 175-185 (1996).
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45. M.J. Yaszemski, R.G. Payne, W.C. Hayes, R. Langer, and A.G. Mikos, "The *In Vitro* Degradation of a Poly(Propylene Fumarate)-Based Composite Material," *Biomaterials, 17,* 2127-2130 (1996).
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